INTERRELATION BETWEEN Pa_{CO_2} AND PA_{CO_2} IN THE CONTROL OF THE MECHANICS OF BREATHING IN MAN*

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THE structural integrity of functioning pulmonary units is not independent of the tension of the respiratory gases. In this respect the importance of carbon dioxide is underlined by the seeming paradox that too little or too much causes bronchoconstriction. The former instance, part of the general theory that tissues isolated from nervous control react to increasing carbon dioxide tension with dilation, was demonstrated by Nisell[1] using isolated lungs and was further emphasized by the experiments of Severinghaus,[2] in which alveolar hypocapnia produced by obstructing pulmonary artery blood flow was followed by bronchoconstriction, subsequently relieved by the administration of carbon dioxide down the airway. Similar results have been obtained in man.[3] The opposite effects were demonstrated in the intact animal; progressive arterial hypercarbia produced by increasing the inspired carbon dioxide tension was followed by increased resistance, decreased compliance, both dynamic and static, and increased work of breathing mediated by the central nervous system via the vagus nerves.[4] However when the values for resistance, compliance, and work are plotted against the range of carbon dioxide investigated (20 to 150 mm.Hg) the resultant curves are seen to change their slopes abruptly in the range 30 to 50 mm.Hg carbon dioxide tension; this suggests that more than one factor is operative.

The use of ventilation mixtures of carbon dioxide in the range of 4 to 10 per cent in dogs[5] and in man[6] did not result in significant changes in resistance and compliance of the lung. However in normal subjects breathing room air then 6 per cent CO_2, Ahmed, Weiss, and Lyons ob-

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served a positive linear relation between alveolar CO_2 concentration and airway conductance.[7]

In view of the contrary effects on the mechanics of respiration that have been reported, our studies were designed to determine in man the magnitude of central versus peripheral control by carbon dioxide tensions within the normal physiological range. The problem facing the investigator is to change selectively the CO_2 in the arterial blood without affecting the alveolar tension, which is ordinarily responsible for the arterial tension. To this end, cross-circulation experiments were accomplished in animals by Daly.[8] Bronchoconstriction resulted when donor venous blood with a high P_{CO_2} was infused into the arterial system of the recipient. The authors however point out that "the changes in cerebral inflow blood gas tension necessary to bring about bronchomotor responses would suggest that they are outside normal physiological range."

We have used the conditions that prevail during cardiopulmonary bypass for this type of investigation in man.[9] When blood flow in the pulmonary artery is stopped during bypass the lungs are functionally isolated. The carbon dioxide tension of the body can be kept constant as the carbon dioxide tension of the alveolar ventilating gas mixture is independently altered. Conversely, by changing the extracorporeal ventilating gas flow rate or adding mixtures of carbon dioxide to the oxygenator, the arterial carbon dioxide tension may be varied while the carbon dioxide in the mixture ventilating the lungs is kept constant.

Methods

Forty patients of both sexes between the ages of 14 and 68 were studied during cardiac operations in which total cardiopulmonary bypass was used. Premedication consisted of secobarbital 50 to 100 mg. and scopolamine 0.4 to 0.5 mg. given intramuscularly 60 min. before induction of anesthesia. Anesthesia was induced with thiopental intravenously, and an endotracheal tube was placed after the administration of 50 to 100 mg. succinylcholine i.v. A fixed volume ventilator was used, set to deliver a peak inspiratory flow rate of 60 l./min. to all of the patients. Anesthesia was maintained with 1 per cent halothane in oxygen. During the bypass interval 1 per cent halothane was administered to the patient via the extracorporeal oxygenator. The heart was approached through a midline sternotomy and the pericardium opened. The pleural spaces were not entered. A roller pump disc oxygenator provided an output of blood of approximately 2.3 $l./m.^2/min$. When total bypass had been attained, blood flow through the pulmonary artery eliminated and left atrial decompression instituted, volume pressure loops were made for the determination of dynamic compliance[10] and work of breathing. Scalar recordings of airway pressure at the mouth, esophageal pressure, tidal volume, and gas flow rate were also made for the determination of airway resistance to gas flow. The concentration of carbon dioxide in the end-tidal gas was monitored continuously by an infrared gas analyzer and the arterial blood carbon dioxide tension was determined with a modified Severinghaus CO_2 electrode.

While ventilation to the oxygenator was kept constant, and the patient's temperature was constant, the arterial carbon dioxide tension was maintained constant as the alveolar ventilating mixture was altered. Airway hypocapnia was produced by ventilating the lung with 100 per cent oxygen and, as there was no route of access to the alveoli for the endogenous carbon dioxide, the end-tidal carbon dioxide rapidly fell to less than 1 per cent. The use of a mixture of 5 to 10 per cent CO_2 in O_2 to ventilate the lungs provided the hypercapnic conditions. In additional groups of patients the reverse study was performed, i.e., the arterial carbon-dioxide tension was changed as the alveolar tension was held at a value constant for each patient. To obtain a low systemic arterial carbon-dioxide tension the oxygenator was ventilated with 100 per cent O_2 at 12 to 14 l./min. After baseline measurements were obtained, the gas ventilating the oxygenator was altered to increase from a low to high arterial carbon dioxide tension by changing to a mixture containing 98 per cent O_2 and 2 per cent CO_2 and reducing the gas flow by 50 per cent (i.e., 6 to 7 l.).

Results

When the arterial carbon dioxide tension was maintained constant (average of 30 mm.Hg) a stepwise change in alveolar carbon dioxide tension from <6 mm.Hg to about 40 mm.Hg produced an increase in compliance of 35 per cent and a decrease of 25 per cent in resistive and of 15 per cent in elastic work of breathing. An alveolar carbon dioxide change of this magnitude produced a decrease of 50 per cent in resistance of pulmonary tissue. These findings indicate a marked degree of hypocapnic-induced constriction, relieved by the addition of CO_2 to

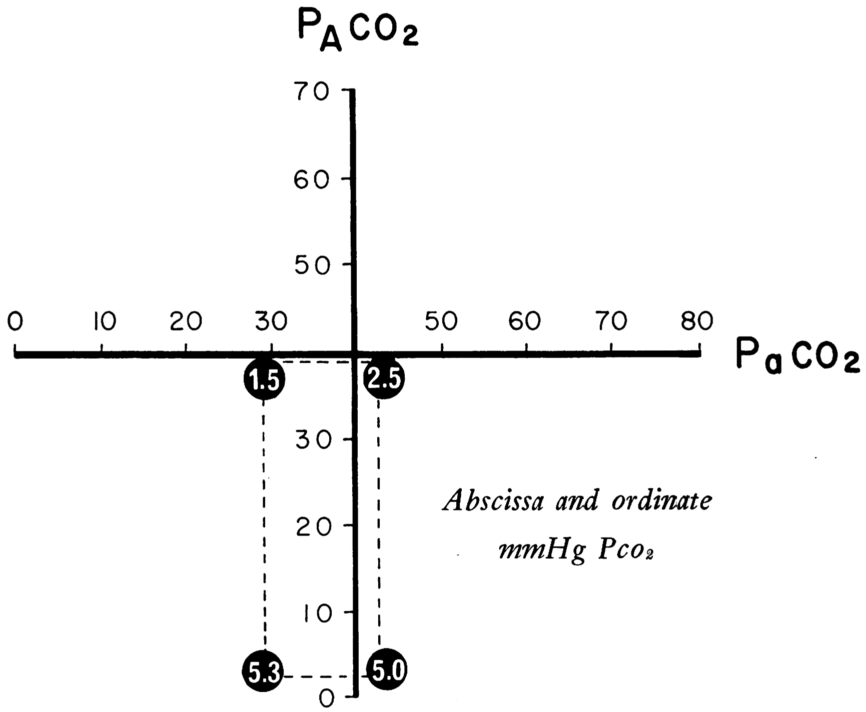

Fig. 1. Dependency of resistance upon the alveolar and arterial carbon dioxide tensions in the individual case. Arterial carbon-dioxide tension shown on the X axis. Alveolar carbon-dioxide tension shown on the Y axis. Within the black dot is the lung-tissue resistance value that was obtained with the varying arterial and alveolar carbon dioxide tensions.

the airway. Such changes came on promptly and were completely reversible upon reversion to the original ventilating mixture. The exact amount by which the values changed appeared to depend upon the arterial carbon dioxide tension which, though maintained constant for each individual, varied among the subjects. In general, the higher the arterial carbon dioxide tension, the greater the per cent change in mechanics.

In the next group of patients the alveolar carbon dioxide tension was held constant during a stepwise increase in arterial carbon dioxide tension. As the alveolar carbon dioxide tension was maintained at less than 6 mm.Hg a stepwise increase of 20 mm.Hg in arterial carbon dioxide tension produced a 25 per cent increase in resistance and a 10 per cent decrease in dynamic compliance. Work values also increased and paralleled the change in resistance to airflow.

When the alveolar CO_2 was maintained constant at a higher level

TABLE.—DEPENDENCY OF RESISTANCE UPON THE ALVEOLAR AND ARTERIAL CARBON DIOXIDE TENSIONS

		$F_{ET\,CO_2}$	
		<1%	6%
$PaCO_2$ mm.Hg	25 18-30)	9.5	3.9
	38 (30-45)	11.0	3.7

Resistance of lung tissue
cm.H_2O/l./sec.

Average values obtained from 10 cases for lung-tissue resistance in cm.H_2O/l./sec. The columns give resistance values when the end tidal carbon dioxide (F ET CO_2) was about 6 mm.Hg tension and when it was about 40 mm.Hg. Reading across the rows gives the resistance values that were obtained when the arterial carbon dioxide tension was 25 mm.Hg (with a range of 18 to 30) or 38 mm.Hg (with a range of 30 to 45).

(48 to 50 mm.Hg) there was less alteration in mechanics in response to a greater change in arterial tension. Thus not only was both a centrally mediated arterial effect and a local peripheral action demonstrated, but it was shown that the magnitude of response of each is dependent upon the level of the other. This is illustrated by subjects who had their arterial carbon dioxide tension increased 10 to 20 mm.Hg at each of two different alveolar levels, i.e., under conditions of airway hypocapnia and hypercapnia or isocapnia. Thus, for example, there would result four values for resistance, and each resistance value could be plotted corresponding to the arterial and alveolar CO_2 tension that existed when the measurement was made. Figure 1 shows the observations made in one such person. Arterial carbon dioxide tensions are shown as abscissas, alveolar carbon dioxide tensions as ordinates. Within the block dot is the resistance value in centimeters of H_2O/l./sec. Thus we see a value for resistance of 1.5 cm.H_2O/l./sec. when the arterial P_{CO_2} is 28 mm.Hg and the alveolar CO_2 is 38 to 40 mm.Hg tension. Maintaining the arterial CO_2 constant but making the airway hypocapnic increases the resistance to 5.3. Such analyses make it quite apparent that resistance values are not independent of both the arterial carbon dioxide tension and the tension within the airway.

In the accompanying table average resistance values for all cases are plotted according to the arterial and alveolar carbon-dioxide tension that existed when the measurement was made. The resistance values are in centimeters of water/l./sec. determined when the airway was

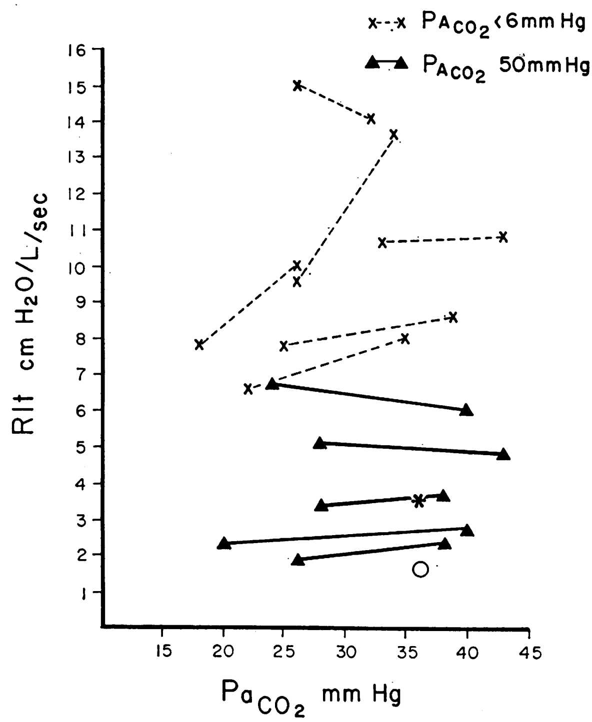

Fig. 2. Effect of change of arterial carbon dioxide tension and of alveolar carbon-dioxide tension on resistance. Values from the same individual are connected by either a solid or dashed line. In each individual the arterial carbon-dioxide tension (X axis) was increased 15 to 20 mm.Hg. The airway during this time was maintained hypocapneic as denoted by the *x*, or isocapneic as denoted by the solid triangles. Our average prebypass value is marked with an asterisk. A normal value for resistance when the arterial carbon dioxide tension is 35 mm. Hg is marked with an open circle.

hypocapnic and when the alveolar CO_2 was greater than 40 mm.Hg and at two different ranges of arterial carbon-dioxide tension; 25 with a range of 18 to 30 and an arterial carbon-dioxide tension of 38 with a range of 30 to 45. The greatest resistance is seen to occur with a high arterial CO_2 tension combined with airway hypocapnia, and the tendency for low resistance values to be associated with high alveolar CO_2 tension is apparent.

Further illustration of these effects is seen in Figure 2, a plot of lung tissue resistance values against arterial carbon dioxide tensions as abscissas. In each individual the arterial carbon-dioxide tension was increased by 15 to 20 mm.Hg; the resulting values for resistance are connected by dashed or solid lines. The airway at the time was maintained either at a low carbon-dioxide tension, less than 1 per cent, denoted by

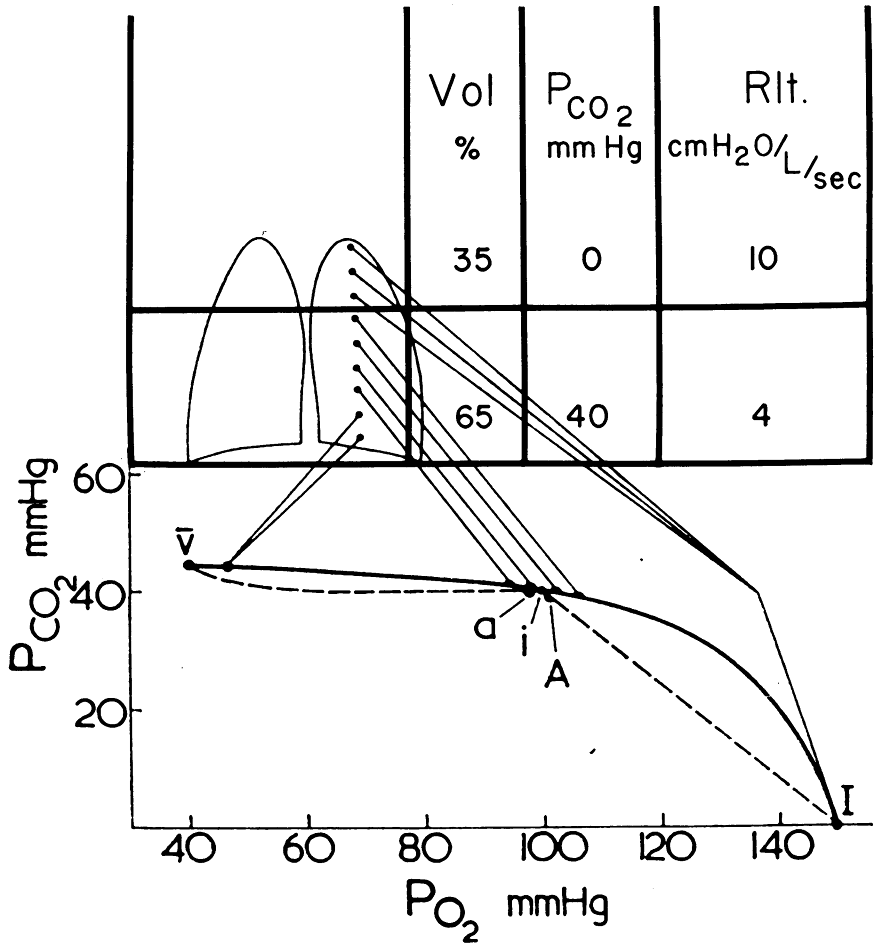

Fig. 3. Schematic pulmonary levels superimposed on a Rahn-Fenn diagram with theoretical gas R lines.[12] The superior portion of the lung as depicted has a high ventilation in relation to perfusion, consequently a low carbon dioxide tension. In these portions a high-resistance, low-compliance, and increased work of breathing would be anticipated.

the *x*, or with a more normal range of tension, about 40 mm.Hg, denoted by the solid triangles. The values fall into two distinct groups according to the level of alveolar carbon-dioxide tension, and the values obtained under conditions of alveolar hypocapnea are far removed from normally occurring values. A normal value for resistance when the arterial carbon-dioxide tension is 35 to 40 mm.Hg is 1.5 to 2.0 cm. H_2O/l./sec.[10] Our subjects, who because of anesthesia, supine position, and associated pulmonary disease would be expected to deviate from normal values, had an average prebypass value for resistance of 3.5 cm. H_2O/l./sec. when the arterial carbon-dioxide tension was 35 mm.Hg.[11]

Similar analyses demonstrate the pronounced effect of alveolar carbon dioxide tension on the maintenance of normal values for the resistive work of breathing, the elastic work of breathing, and for dynamic compliance in the 35 to 40 mm.Hg range.

Discussion and Summary

Superimposing schematic pulmonary levels on the Rahn Fenn diagram as used by West[12] is a useful aid to visualizing the resultant effects of changes in ventilation and perfusion. Normally the gas R lines are grouped around the ideal, alveolar, and arterial points. Hemorrhage, anesthesia, positive pressure breathing, and other causes of pulmonary hypotension swing the gas R lines to the right, more and more approaching the inspired point with high alveolar ventilation to perfusion ratios. Such portions of the lung are hypocapnic and would be expected to have increased resistance and decreased compliance and to be associated with an increased work of breathing in contrast to other portions of the lung with low ventilation to perfusion ratios and higher airway carbon dioxide tensions (Figure 3).

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